

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**

IN RE PFIZER INC. SECURITIES LITIGATION	X : : : : : X	No. 04-CV-9866 (LTS) ECF CASE
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PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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INTRODUCTION

After the denial by this Court of their motion to dismiss, Defendants, in a September 11, 2008 letter to this Court, suggested an early hearing on whether Plaintiffs would be permitted to present to the trier of fact expert testimony regarding the cardiovascular (“CV”)¹ risk of Celebrex and/or Bextra. PX 164; Tr. 197:19-25, 201:1-7. In that letter, Defendants did not limit consideration of the risks at issue to only those that could be characterized as thrombotic or thromboembolic events. PX 164. In fact, the words “thrombotic” and “thromboembolic” do not appear anywhere in Defendants’ letter. *Id.* In response, Plaintiffs argued that a *Daubert* hearing would be premature prior to discovery. Tr. 209:10-210:1. Plaintiffs did not have the opportunity to proffer expert reports in the subject area of their choosing, rather, Defendants insisted that Plaintiffs should provide reports on increased cardiovascular risk prior to full discovery. *Id.*

At the September 18, 2008 conference, the Court determined that the Plaintiffs would be required to provide expert reports and prepare for a hearing on “the question of whether there was in existence, on or prior to [December 2004] information, that as a scientific matter was sufficiently significant to trigger a disclosure obligation under the securities laws as to a cardiovascular risk related to [Celebrex and Bextra].” PX 166 at 14:4-10. At a subsequent hearing on December 1, 2008, the Court reiterated its earlier conclusion and indicated that Plaintiffs’ experts were to opine on whether there existed “study results [that], as a scientific matter, prior to December 16, 2004, demonstrated a scientifically significant risk of cardiovascular incidents associated with Celebrex [and Bextra].” PX 169 at 18:24-19:2. Thus, when requesting the *Daubert* hearing, Defendants framed the issue in general terms as “CV risk” and this is the issue the Court directed Plaintiffs to address.

¹ See Appendix “A” for definitions of selected terms and acronyms.

In response to the Court's directive, Plaintiffs submitted a number of expert reports, Defendants submitted reply expert reports, and Plaintiffs submitted rebuttal reports. The parties then engaged in extensive expert deposition discovery.

After reviewing Plaintiffs' expert reports and the results of expert discovery, Defendants have now attempted to redefine the relevant inquiry, contending that Plaintiffs' experts have not offered "reliable evidence of an increased thrombotic risk before a certain date." Tr. 12:8-9. While Defendants are free to seek exclusion of any testimony they wish, Plaintiffs experts focused their opinions on the issue framed by the Court (notably, at Defendants' urging), that is whether evidence existed prior to December 2004, that Celebrex and Bextra increased the risk of CV events. PX 174 at ¶ 20(a)(b) (Furberg March, 2009 Expt. Rpt); PX 176 at 3 (Kronmal March, 2009 Expt. Rpt); PX 175 at ¶ 2 (Madigan March, 2009 Expt. Rpt.). Accordingly, Defendants' effort to exclude Plaintiffs' experts opinions by emphasizing "thrombotic" risk should be denied as Plaintiffs experts did not offer any opinions on that issue.

OVERVIEW OF EXPERT OPINIONS

In response to the questions set forth by this Court regarding whether there existed, prior to December 16, 2004, "a scientifically significant risk of cardiovascular incidents" associated with Celebrex and/or Bextra, Plaintiffs submitted reports by three primary experts.² Two of Plaintiffs' experts (Dr. Curt Furberg and Dr. Richard Kronmal) looked at the individual study data that was available to Pfizer, while the third (Dr. David Madigan) conducted a meta-analysis of all of the study data available. Specifically:

- Dr. Furberg conducted a review of the medical literature and clinical studies for Celebrex and Bextra, and utilizing the same methods employed by the Food and Drug Administration ("FDA") medical officers to perform safety reviews, confirmed the scientific significance of the information in Pfizer's possession concerning CV risk as early as 1999 (*see infra* § I);

² A fourth report, by Dr. Joel Bennett, is not being relied upon by Plaintiffs.

- Dr. Kronmal conducted his own analysis of Pfizer's clinical trial data (utilizing the SAS data files produced by Pfizer in this litigation), including Celebrex osteoarthritis/rheumatoid arthritis ("OA/RA") studies, the Alzheimer's study and a number of other Celebrex and Bextra studies, and determined that, from a safety perspective, there was statistically significant evidence of CV risk associated with Celebrex and Bextra prior to December 2004 (*see infra* § II); and
- Dr. Madigan employed reliable and accepted statistical methods to construct a meta-analysis based on the same data and endpoints developed by Pfizer.³ Dr. Madigan conducted a meta-analysis to provide a composite view of multiple studies over time to determine when Pfizer was or should have been aware of the increased CV risk. Dr. Madigan's analysis demonstrated statistically significant elevated risk for Celebrex for each year, starting as early as 1999 (*see infra* § III).

After submission of their expert reports, Plaintiffs discovered two meta-analyses that had been prepared by Pfizer, one immediately preceding and the next immediately following the Class Period. These two analyses were buried in the 36 million pages of documents produced by Pfizer and both fully corroborated the statistical conclusions of Drs. Kronmal and Madigan. The meta-analyses included: (i) an internal Pfizer meta-analysis from 1999 of the OA/RA studies on Celebrex (the "1999 Safety Memo") that showed a statistically significant CV risk (PX 1270), and (ii) a 2005 Meta-Analysis based on study results Pfizer possessed during the Class Period, provided by Pfizer to the FDA and other regulatory bodies (the "Pfizer 2005 Meta-Analysis"), reflecting that Celebrex had a 7.07 times greater risk of certain CV events (at a p-value of 0.035) than did placebo, a highly statistically significant finding. PX 106 at Cele IND 48395 00008058.

In an effort to contradict the conclusions of Plaintiffs' experts (which agreed with Pfizer's own analyses), Defendants primarily rely upon the opinion of Dr. Lee-Jen Wei, whose meta-analysis purportedly demonstrates that there was no reliable evidence of increased

³ In his analysis, Dr. Madigan used Pfizer-developed endpoints, which Pfizer used in multiple regulatory submissions including its own 2005 meta-analysis. This meta-analysis was submitted to the FDA and other governmental regulatory agencies to address CV safety issues of Cox-2 inhibitors, thus, these endpoints reflect what Pfizer itself determined were reasonable and reliable means to assess these issues.. Tr. 463:7-13, 536:1-6, 638:25-639:5, 866:8-10; PX 761 at ¶¶ 8-9; PX 1240 at EMEA 10000017693; PX 1257 at 7-8, 16-17.

thrombotic risk associated with Celebrex or Bextra prior to December 16, 2004. PX 134 at ¶ 8. Dr. Wei's analysis, however, was fatally flawed. First, the Pfizer-adjudicated data set he utilized was not created until 2007, and thus, could not have been used by Pfizer in any of its analyses during the Class Period. *See infra* § IV.B. Second, as shown by Plaintiffs' expert Dr. Nicholas Jewell, Dr. Wei also employed several unreliable statistical methods that specifically mask the true CV risk associated with Celebrex and Bextra. *See infra* § V.C. Finally, due to a purported "calculation error," Dr. Wei withdrew 23 separate schedules representing the entirety of his analyses of Dr. Madigan's data and endpoints. *See infra* § V.A. As a result, Wei offers no opinion that provides any information regarding what information was available to Pfizer regarding CV risk of Celebrex and Bextra during the Class Period. The flaws in Wei's opinions adversely impact the other Defense Experts, who rely heavily on his analyses.

PROPOSED CONCLUSIONS OF LAW

1. The admissibility of expert testimony is governed by Federal Rule of Evidence 702 ("Rule 702") as elucidated by the Supreme Court's decisions in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993) ("*Daubert*"), and its progeny. *Stone v. 866 3rd Next Generation Hotel, LLC*, No. 99 Civ. 4780 (LTS), 2002 WL 1046706, at *1 (S.D.N.Y. May 22, 2002).

2. Rule 702 provides:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702.

3. The Second Circuit directs district courts to fulfill their gate-keeping role under *Daubert* by making several determinations before allowing expert testimony: (1) whether the witness is qualified to be an expert; (2) whether the opinion is based upon reliable data and methodology; and (3) whether the expert's testimony on a particular issue will assist the trier of fact. *See Nimely v. City of New York*, 414 F.3d 381, 396-97 (2d Cir. 2005). "[T]he Rule's basic standard of relevance ... is a liberal one." *Daubert*, 509 U.S. at 587.⁴

4. Courts should not prejudge the weight of conflicting evidence, the credibility of the witnesses, or substitute the judgment of the court for that of the jury. *See In re Joint E. & S. Dist. Asbestos Litig.*, 52 F.3d 1124, 1133 (2d Cir. 1995); *see also Johnson & Johnson Vision Care, Inc. v. CIBA Vision Corp.*, No. 04 Civ. 7369 (LTS), 2006 WL 2128785 at *7 (S.D.N.Y. July 28, 2006) (noting that admissibility is warranted even when assumptions upon which an expert bases her analysis are "ill-formed or inconsistent with other evidence"). Such arguments "go to the weight of the testimony rather than the quality of the expertise or the reliability of the economic methodology." *Id.*

5. Because of the liberal admissibility rules under Rule 702 and *Daubert*, an expert's testimony can be excluded altogether only if it "amount[s] to the sort of 'junk science' *Daubert* blocks." *Skidmore v. Precision Printing & Packaging, Inc.*, 188 F.3d 606, 618 (5th Cir. 1999).

6. "Only if the expert's opinion is so fundamentally unsupported that it can offer no assistance to the jury must such testimony be excluded." *In re Neurontin Mktg., Sales Practices*,

⁴ *See also Nimely*, 414 F.3d at 395 ("Rule 702 embodies a liberal standard of admissibility for expert opinions."); *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 282 (E.D.N.Y. 2007) ("[T]he assumption the court starts with is that a well qualified expert's testimony is admissible.").

and Prods. Liab. Litig., 612 F. Supp. 2d 116 (D. Mass. 2009) (quoting *Bonner v. ISP Techs., Inc.*, 259 F.3d 924, 929-30 (8th Cir. 2001)).

A. QUALIFICATIONS OF THE EXPERT

7. The qualifications of the expert are relevant not only to the qualifications prong of Rule 702, but the reliability of the expert: “the more qualified the expert, the more likely that expert is using reliable methods in a reliable manner – highly qualified and respected experts don’t get to be so by using unreliable methods or conducting research in an unreliable manner.” *Malletier v. Dooney & Bourke, Inc.*, 525 F. Supp. 2d 576, 616 (S.D.N.Y. 2007).

B. RELIABILITY OF THE DATA

8. Determinations regarding the sufficiency of facts and data “are inherently fact specific.” *Melini v. 71st Lexington Corp.*, 07 Civ. 701 (JCF), 2009 WL 413608, at *6 (S.D.N.Y. Feb. 13, 2009).

9. Aside from the sufficiency of “facts and data,” the *Daubert* Court “has identified a number of factors bearing on reliability that district courts may consider, such as: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication;⁵ (3) a technique’s known or potential rate of error, and the existence and maintenance of standards controlling the technique’s operation; and (4) whether a particular technique or theory has gained general acceptance in the relevant scientific community.” *Amorgianos v. Nat’l R.R. Passenger Corp.*, 303 F.3d 256, 266 (2d Cir. 2002) (citations omitted); *accord Nimely*, 414 F.3d at 396. However, this “list of factors was meant to be helpful, not definitive,” and “neither necessarily nor exclusively applies to all experts or in every case.” *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 141, 151 (1999).

C. ASSISTANCE TO THE TRIER OF FACT OR “FIT”

10. Courts conducting a *Daubert* inquiry must also ascertain whether the expert testimony will assist the trier of fact in understanding or determining a fact in issue. This inquiry “essentially asks whether the expert’s testimony ‘fits’ the facts of the case,” *Graham v. Playtex Prods. Inc.*, 993 F. Supp. 127, 130 (N.D.N.Y. 1998) (citing *Daubert*, 509 U.S. at 591); has a valid “connection to the pertinent inquiry”; and is “sufficiently tied to the facts of the case so that it will aid the jury in resolving a factual dispute.” *Adesina v. Aladan Corp.*, 438 F. Supp. 2d 329, 341-42 (S.D.N.Y. 2006) (quoting *Daubert*, 509 U.S. at 591-592).

D. MINOR METHODOLOGICAL FLAWS, ERRORS IN CALCULATION, AND ARGUMENTS ABOUT ASSUMPTIONS OR CREDIBILITY GO TO WEIGHT, NOT ADMISSIBILITY

11. The district court’s inquiry under *Daubert* “is not intended to replace the adversary system.” *Colon v. BIC USA, Inc.*, 199 F. Supp. 2d 53, 75 (S.D.N.Y. 2001); *see also Amorgianos*, 303 F.3d at 267 (“[O]ur adversary system provides the necessary tools for challenging reliable, albeit debatable, expert testimony.”). Thus, a “minor flaw in an expert’s reasoning or a slight modification of an otherwise reliable method will not render an expert’s opinion *per se* inadmissible.” *Amorgianos*, 303 F.3d at 267; *see also Johnson & Johnson Vision Care*, 2006 WL 2128785, at *7 (citing *McCulloch v. H.B. Fuller Co.*, 61 F.3d 1038 at 1044 (2d Cir. 2000); *Latino Officers Ass’n v. City of New York*, No. 99 Civ. 9568 (LAK), 2003 WL 21638165, at *2 (S.D.N.Y. July 14, 2003); *Daubert*, 509 U.S. at 596).

⁵ “[I]t is well settled that publication is but one element of peer review and ‘does not necessarily correlate with reliability.’” *Johnson & Johnson Vision Care*, 2006 WL 2128785, at *7 (citing *Daubert*, 509 U.S. at 593 and *FDIC v. Suna Assocs., Inc.*, 80 F.3d 681, 687 (2d Cir. 1996)).

PROPOSED FINDINGS OF FACT

I. CURT FURBERG

A. DR. FURBERG'S TRAINING, EDUCATION AND EXPERIENCE

12. Dr. Curt D. Furberg has more than 30 years of experience in the field of drug safety and clinical trial research, including clinical trial event adjudication. PX 174 at ¶ 5; Tr. at 189:17-190:3, 275:15-19. He is a national leader in CV epidemiology, and has been a lead investigator for a number of clinical trials of agents affecting the CV system, including aspirin. Tr. 84:22-85:10, 86:22-87:15; PX 203 at 349:14-22; PX 174 at ¶ 5a.

13. Dr. Furberg's experience includes (a) 11 years of research at the prestigious National Institutes of Health ("NIH") National Heart, Lung, and Blood Institute, Tr. 86:22-87:15; PX 174 at ¶ 1; and (b) 10 years as the Chairman of the Department of Public Health Sciences at the Wake Forest University School of Medicine, overseeing the Epidemiology, Biostatistics, and Social Sciences and Health Policy Sections. Tr. 87:18-23; PX 174 at ¶ 4, App. A at 2.

14. Dr. Furberg: (a) has been a member of Data Safety Monitoring Committees for more than 50 clinical trials, sponsored by private and public entities such as the NIH and the pharmaceutical industry (including Pfizer), Tr. 95:21-96:4; PX 174 at ¶ 5b, App. A at 5-6; (b) is a frequent consultant to academic institutions, pharmaceutical companies, and government agencies on clinical trial design and safety issues, Tr. 94:17-22, 95:24-96:14; PX 174 at ¶ 5c; (c) was a Charter Member of the FDA Drug Safety and Risk Management Advisory Committee (2001-2006) and an invited member of the FDA Advisory Committee on the Safety of Selective COX-2 Inhibitors (February 2005), Tr. 103:6-22; PX 99 Part 1 Vol. 1 at 1-2, 6, 11; (d) co-authored the American Heart Association ("AHA") position paper on the CV risks of COX-2 drugs, Tr. 134:22-135:3, PX 128 at 1634; and (e) was retained by Pfizer in 1999, to assess the *cardiovascular safety of Celebrex*. Tr. 83:10-22; PX 174 at ¶ 33 (emphasis added).

15. Dr. Furberg continues to: (a) advise the FDA; (b) serve as a frequent consultant to the World Health Organization (“WHO”); and (c) serve as an invited expert on drug safety (including testifying at Congressional Hearings held March 2005 and March 2007). Tr. 93:23 – 94:6, 96:5–97:4; PX 174 at ¶ 5c, 8; Furberg Dem. F-4a.

16. Dr. Furberg has authored or co-authored more than 380 peer-reviewed articles (approximately 70 of which are on drug safety) and sixty (60) book chapters on topics including epidemiology, clinical trials, non-steroidal anti-inflammatory drugs (“NSAIDs”, including COX-2 inhibitors) and hypertension. Tr. 91:3-8; PX 174 at ¶ 14. Dr. Furberg co-authored a leading textbook on clinical trials entitled *Fundamentals of Clinical Trials*, as well as *Data Monitoring in Clinical Trials—A Case Studies Approach* (2006) and *Evaluating Clinical Research—All that Glitters is not Gold* (2007). Tr. 90:10-18, 91:9-21; PX 174 at ¶¶ 12, 13.

B. DR. FURBERG’S OPINIONS ARE BASED ON RELIABLE DATA AND METHODS

17. Dr. Furberg was asked to examine the individual results of major Pfizer clinical trials – whether or not statistically significant – to evaluate whether there was information that demonstrated a scientifically significant risk of adverse cardiovascular events associated with the use of Celebrex and Bextra prior to December 16, 2004. PX 174 at ¶ 17; *see also* PX 169 at 18:21-19:6.

18. In addressing the information available to Pfizer on the CV risks posed by use of Celebrex and/or Bextra (*see* PX 174 at ¶ 17; *see also* PX 169 at 18:21-19:6), Dr. Furberg conducted a review of the medical literature and clinical studies for Bextra and Celebrex in order to determine at what point, if any, safety concerns arose regarding Celebrex and/or Bextra. Tr. 105:7-13, 107:1-4; PX 174 at ¶¶ 17-18. This type of literature review is the “time honored” method for surveying and synthesizing research findings. *See* PX 21 at 380.

19. The Heart Failure Society has stated that randomized controlled clinical trials are "A" level evidence for drug evaluation. Tr. 105:20-106:5; PX 115 at 3. Dr. Furberg similarly considers a randomized clinical trial to be the "gold standard" in terms of evaluating drugs. Tr. 105:9-12, 106:1-11. Defense Experts Drs. Massie and Wei agree. PX 201 at 429:8-15; PX 181 at ¶ 23.

20. Further, the results of even a single randomized controlled clinical trial study (such as the Alzheimer's 001 study, *infra*) should not be dismissed in favor of a meta-analysis, particularly where the study involved a vulnerable patient population. As noted by the FDA:

a finding from a single study should not be automatically dismissed because of the results of a pooled analysis, especially if it is detected in a study of superior design or in a different [patient] population . . . sponsors should present risk information that details the range of results observed in individual studies, rather than producing a summary value from a pooled analysis.

PX 98 at VI. D (FDA PREMARKETING RISK ASSESSMENT).

21. Dr. Furberg did not analyze every study involving Bextra and Celebrex. As noted by the FDA, early preapproval trials (e.g., Phase 1 and Phase 2 trials) rarely provide meaningful safety data because such studies typically are not designed to evaluate safety and are too small in duration and size to detect a safety issue for a given agent. PX 189 at 2-3; PX 76 at 4,-5; Tr. 111:25-113:4. Additionally, preapproval studies often involve healthier patient populations than those that will be taking the drug once it is released to market. PX 76 at 4-5; PX 98 at 23; Furberg Dem. F-11. Consistent with this view, Dr. Furberg's analysis focused on larger studies, often of a longer duration, and/or which involved more vulnerable patient populations, as such clinical trials were far more likely to provide meaningful safety information. Tr. 119:4-120:5, 246:12-18, 258:18-259:2, 260:21-261:10; PX 192 at 43:14-45:25.

22. Accordingly, Dr. Furberg reviewed all significant clinical trials regarding Celebrex and Bextra – *i.e.*, those in which there were adverse events that would provide

information regarding the risks posed by use of Celebrex and Bextra. Tr. 104:22-105:6, 143:8-19; *see also* Tr. 102:1-12, 150:25-151:4, 152:19-153:6, 157:19-23; 160:4-6. Dr. Furberg's methods required him to place the greatest weight on those trials with the most adverse events. PX 192 at 58:8-24; Tr. 125:15-126:5.

23. Under Dr. Furberg's methodology, and consistent with FDA guidance and practice, whether a clinical trial provides information about safety issues with a drug does not hinge on whether the results of the study achieve some pre-specified level of "statistical significance," *i.e.*, the probability that the adverse event is due to chance versus causal association. PX 174 at ¶ 28(e), PX 192 at 329:5-23. In evaluating whether the identified studies provided evidence of increased CV risk, Dr. Furberg relied on statistical comparisons of CV events between Bextra and Celebrex and the respective study control arms. PX 174 at ¶¶ 43(b), 45(e). The statistical comparisons reflect the error rate and uncertainty associated with the comparison, all of which are reproducible and subject to verification using methods generally accepted within the relevant scientific community. Tr. 382:17-383:3.

24. Indeed, as Dr. Furberg testified, while he did find statistically significant evidence of an increased risk of cardiovascular events for both Bextra and Celebrex, he also found significant (albeit not statistically significant) differences in the incidence of certain cardiovascular events in a number of clinical trials involving Bextra and Celebrex. PX 174 at ¶ 20(a). *See also* Tr. 121:15-122:14. Defendants' own expert Dr. Massie, in his expert report, specifically acknowledges that:

[a] trial that does not yield a statistically significant result may yield important information about the relationship between a medication and a certain adverse effect ... A non-significant finding also could indicate that the trial was not large enough or did not yield enough events to detect a meaningful difference.

PX 154 at 7.

25. The FDA agrees that a safety finding from a clinical trial need not be statistically significant in order to warrant a label change such as a precaution or warning. *See* 21 C.F.R. § 201.57(c)(6). Nor does the agency require statistical significance before withdrawing a drug from the market. Tr. 122:15-18; PX 189 at 4; *see also* PX 88.

26. The above methods used by Dr. Furberg in assessing the information available to Pfizer concerning the risks posed by Celebrex and/or Bextra – which primarily involve the analysis of both statistically significant and non-statistically significant placebo controlled clinical trials, with emphasis on the trials with the largest number of events – are the same as those utilized by FDA medical officers when conducting safety reviews. Tr. 94:7-13, 119:22-120:5; PX 76 at 2, n.3. They also are the same methods that Dr. Furberg used when working on the FDA committee that reviewed COX-2 drugs. Tr. 168:10-13.

C. DR. FURBERG RELIABLY APPLIED THE METHODS TO THE DATA

1. Information Available To Pfizer From Its Own Studies Regarding The CV Risks Of Celebrex

27. Dr. Furberg extensively testified regarding the information that Pfizer had available to it regarding the CV risks of Celebrex from its internal clinical studies. *See, e.g.*, Tr. 138:13-139:4, 143:8-21, 146:17-22, 150:25-151:24, 158:10-159:8, 104:8-18, 171:13-2.

28. As early as July 14, 1999, Pfizer completed a meta-analysis of the OA/RA clinical trials that Pfizer used to obtain Celebrex approval. These trials showed that those taking Celebrex at 100 and 200 mg had a significantly increased chance of experiencing a CV event (178 Celebrex events compared to 55 on placebo) – a statistically significant result with a p-value of < 0.001. Tr. 148:4-149:15; PX 1270 at 6; Furberg Dem. F-20.

29. This same meta-analysis showed a statistically significant increase in CV events with Celebrex at 400 mg (17 CV events as opposed to 7 in the placebo group). Tr. 149:8-15; PX

1270 at 7; Furberg Dem. F-20. Similarly, when looking at myocardial infarctions, Celebrex showed 7 events while the placebo group had 1, which again is statistically significant. Tr. 149:17-150:13; Furberg Dem. F-20. When examining the breakdown of the CV events, the older population taking Celebrex had more statistically significant adverse events than the placebo group. Tr. 150:2-23.

30. The Alzheimer's Study (IQ5-97-02-001, referred to as the "Alzheimer's Study" or "ALZ-001"), initiated in July 1997, was a 52-week study designed to assess whether treatment with Celebrex 200 mg twice daily would limit or attenuate the progression of Alzheimer's disease. PX 433 part 2 at 3. ALZ-001 was a double-blind placebo-controlled trial with 285 patients in the Celebrex treatment arm and 140 patients in the placebo treatment arm (425 patients total) in a 2:1 ratio with a mean age of 73 years. PX 433 part 2 at 3, 8; Tr. 142:22-23. It was completed on June 24, 1999. PX 433 part 2 at 1.

31. Because the ALZ-001 study was conducted in a population at high risk for CV events and had a follow-up time of one year, it is well-suited for determining the CV risk of Celebrex. PX 174 at ¶ 31. In addition, there was extensive patient follow-up and any minor lack of follow-up was similar in the two treatment arms. PX 176 at 21, Tr. 325:19-326:2.

32. Dr. Furberg reviewed the ALZ-001 data. He relied on generally accepted end points and, in fact, the events that he analyzed were the same ones *selected and reported by Pfizer* to the FDA and the medical community. Tr. 326:9-12; PX 192 at 146-48, PX 81 at 6.

33. Based on this review, he found a statistically significant difference in CV events in the ALZ-001 trial. Tr. 143:8-19. He concluded that "the combined incidence of serious adverse CV events was significantly higher in the Celebrex group compared to placebo 7.7% vs. 2.1% (p = 0.03)." PX 174 at ¶ 31. He further concluded that: "The rate of CV deaths in the

Celebrex group was more than twice that in the placebo group (9/285 vs. 2/140).” *Id.* Pfizer itself, in the first public reporting of these events (years after the study was completed), ***conceded that the difference in CV-related adverse events was statistically significant.*** PX 81 at 6; Tr. 143:23-144:15.

34. In December 2004, the co-chairs of the Data Safety Monitoring Board (“DSMB”) for the ALZ-001 study wrote Pfizer regarding their concerns about the CV events in that trial, and Pfizer’s failure to previously publish the results. Tr. 331:25-332:13; PX 74. In this letter, the DSMB co-chairs described their concerns about an excess rate of cardiac events in the Celebrex treatment arm when compared to the placebo treatment arm. *Id.* Dr. Furberg reviewed this information in reaching his opinions in this case. PX 174 at ¶ 31.

35. In light of the risks, the DSMB co-chairs explained that the ALZ-001 study ***“should have been fully published in 2000, and perhaps if it had been some attention might have been drawn to potential safety issues.”*** PX 74 at 3 (emphasis added).

36. After the concerns had been raised by the DSMB, Pfizer provided an updated report on the ALZ-001 study to the FDA on January 5, 2005. PX 72.

37. Although the study was completed in 1999, the results were not published in a scientific journal until October 26, 2006, seven years later. PX 129.

38. Another large active comparator trial completed in 2000 was Pfizers Successive Celebrex Efficacy and Safety (“SUCCESS”) trial. Tr. 151:5-152:17. This trial randomized 4,393 participants to Celebrex 100 mg twice daily, 4,407 participants to Celebrex 200 mg twice daily, 905 participants to Naproxen 500 mg twice daily, and 3,489 participants to diclofenac 50 mg twice daily. PX 66 at 3. The duration of the SUCCESS trial was 12 weeks. PX 66 at 4.

Like the ALZ-001 trial results, the full results of the SUCCESS study were not published until 2006, long after the CV risks of Celebrex became widely known. PX 119 at 225; Tr. 151:20-24.

39. In Table 6 of the SUCCESS study, the number of myocardial infarctions (“MIs”) in the Celebrex group is reported as 10 (0.55 per person-year) and for the combined Naproxen/diclofenac group there was 1 reported MI (0.11 per person-year). PX 119 at 262. Thus, the relative risk “RR” for MIs with Celebrex compared to the combined comparator group is 4.99 (95% confidence interval 0.78-31.73; p-value 0.09). PX 176 at 24. In other words, Celebrex patients were almost five times more likely to suffer an adverse CV event. PX 174 at ¶ 37(b); Tr. 151:18-24; PX 119 at 262.

40. On February 18, 2005, in a unanimous decision, the 32 members of the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 32-0 that the available data supported a conclusion that Celebrex significantly increased the risk of CV events. Tr. 153:10-17; PX 99 at Vol. III. at 165, 184-86.

41. Moreover, the Pfizer 2005 Meta-Analysis found that Celebrex, at doses of 400 mg per day, was 7.07 times more likely than placebo to cause adverse CV events. PX 106 at Cele IND 48395 00008058.

2. Information Available To Pfizer From Its Own Studies Regarding The CV Risks Of Bextra

42. Dr. Furberg reviewed a number of Bextra clinical trials and found that Pfizer had available to it information about the increased CV risk Bextra posed long before December 2004. For example, the Bextra study N91-97-02-016 (“Study 016”) available in June 25, 1998, compared Bextra to Naproxen and placebo in a six-week study where 70-80% of the patients were women (and thus less likely to suffer a heart attack). Tr. 140:22-141:5; Furberg Dem. F-23. The adverse CV results of Study 016 were not statistically significant, but showed six heart

attacks for patients taking Bextra versus zero heart attacks for patients taking naproxen or placebo. Tr. 141:14-142:4.

43. Dr. Furberg also reviewed Bextra study N91-99-02-047 (“Study 047”), which was a Bextra clinical trial in patients with osteoarthritis and rheumatoid arthritis. PX 174 at ¶ 43(d). The results, available to Pfizer in 2000, showed that patients taking 40 mg of Bextra twice per day were significantly more likely to develop hypertension than patients taking Naproxen. *Id.* Specifically, 9.2% of patients taking Bextra developed hypertension compared to only 4.6% of patients taking Naproxen, determined by Pfizer to be statistically significant at the 0.05 level. PX 30 at 73. An internal Pfizer document quotes Dr. Needleman (the scientist most responsible for creation of COX-2 inhibitors), of Pfizer’s predecessor Pharmacia, as stating, “***To me it looks like a small but annoying [safety] signal is present.*** I think we should continue taking all kinds of cuts at this [data] and preparing for the FDA review and battles that might occur.” PX 29 at Verburg-K 1000106444 (emphasis added). Another internal document shows that on October 3, 2000, Ethan Weiner, of Pfizer, recognized that “***The safety profile looks very Vioxx-like in my opinion.***” PX 27 (emphasis added). Despite Pfizer’s concerns about the safety of Bextra as a result of Study 047, Pfizer never published it in peer-reviewed literature. Tr. 31:1-4; PX 174 ¶ 43(d). Dr. Furberg opined that Study 047 is evidence of the harmful CV effects of Bextra. PX 174 at ¶ 43(d); PX 192 at 253:21-256:2.

44. In the summer of 2000, Pfizer completed study I93-99-02-035, a clinical trial generally referred to as the “CABG-I” study. PX 26 at 3. CABG-I evaluated the safety of parecoxib (the intravenous form of valdecoxib (Bextra)) followed by oral valdecoxib, compared to placebo in 462 patients who had undergone coronary artery bypass surgery (“CABG”). *Id.* at 7. The results revealed a statistically significant greater incidence of CV/thromboembolic

events, including MI, in the parecoxib/valdecoxib treatment group compared to the placebo/placebo treatment group. PX 174 at ¶ 43(b); PX 26 at 77; PX 779 at 5.

45. The results of CABG-I were not published until June 2003 (*i.e.*, three years after trial completion in the summer of 2000). PX 174 ¶ 43(b).

46. In 2003, Pfizer initiated a second study, PARA-0505-071, with parecoxib and valdecoxib in patients following CABG surgery generally referred to as the “CABG-II” study. PX 67 at 1; PX 174 at ¶ 52. The CABG-II results confirmed the safety problems observed in CABG-I, specifically, adverse events were twice as common in the Bextra group as compared to placebo (7.4% vs. 4.0%, $p=0.02$), as well as a statistically significant excess risk of major cardiovascular events among Bextra users (2% vs. 0.5%, $p=0.03$). PX 174 at ¶ 52; PX 67 at 13.

47. Shortly after the news of the CABG-II trial was released, Dr. Furberg performed a pooled analysis of the two trials, CABG-I and CABG-II, which was reported at the annual meeting of the American Heart Association in November 2004, and published in the journal CIRCULATION in early 2005. PX 78. The analysis of CABG-I and CABG-II, based on the reported data, demonstrated that Bextra caused a statistically significant ***three-fold increased risk*** (as compared to placebo) of major CV events (coronary and cerebrovascular), 2.2% vs. 0.7%. PX 174 at ¶ 53; Tr. 160:15-24, 163:24-164:24; PX 78.

3. Information From Outside Sources That Was Available To Pfizer Regarding The CV Risks Of COX-2 Drugs

48. In addition to Pfizer’s own internal data on Celebrex and Bextra (discussed above), Dr. Furberg analyzed a wealth of other information available to Pfizer regarding the adverse CV effects of COX-2 drugs. Tr. 105:7-107:16; *see also* Appendix B hereto (Timeline, Furberg Dem. F-43). As early as 1998, as a result of the presentation of a paper to the American Association for Advancement of Science setting forth the “FitzGerald Hypothesis” (a theory as

to why selective COX-2 inhibition could cause an increased risk of CV events), there was information available to Pfizer regarding the CV risks of Celebrex and Bextra. Tr. 138:13-139:4, PX 174 at ¶ 33; PX 1117. Pfizer itself called the FitzGerald Hypothesis “credible.” PX 248 at 2.

49. By March 2000, as a result of Merck’s publication of data from the Vioxx Gastrointestinal Outcome Research trial (“VIGOR”), Pfizer had further information available to it regarding the adverse CV effects of COX-2 drugs as the VIGOR trial showed a 5-fold increase in heart attacks for users of Vioxx (Merck’s COX-2 drug). Tr. 153:24-154:23; PX 212 at 5.

50. In 2001, Dr. Eric Topol published a paper in the Journal of the American Medical Association (the world’s largest circulation medical journal) examining four clinical trials of COX-2 inhibitors, and concluded that both Vioxx and Celebrex increased the risk of heart attacks. Tr. 154:24-156:16; PX 38.

51. In 2003, the European Medicines Agency (“EMA”) recommended a warning be added to the Celebrex label. Tr. 156:18-157:8. In February 2005, the EMA’s Committee for Medicinal Products for Human Use found “an increased risk of CV adverse events for COX-2 inhibitors as a class” and recommended that “[selective COX-2 inhibitors] should not be used in patients with ischemic heart disease or stroke.” PX 94 at 1-2.

52. In 2006, Dr. Kearney and others put forth a meta-analysis that demonstrated a class effect for increased CV events among all COX-2 inhibitors, including Celebrex and Bextra. Tr. 170:14-172:17; PX 113.

D. DR. FURBERG’S CONCLUSION – THAT THERE WAS AVAILABLE TO PFIZER STATISTICALLY SIGNIFICANT EVIDENCE ON THE CV SAFETY ISSUES WITH CELEBREX AND BEXTRA AS EARLY AS MID-1999 – SATISFIES THE *DAUBERT* FIT REQUIREMENT

53. All of the above information was relevant to Dr. Furberg’s review because he takes a broad view when looking at safety. Tr. 104:19-25. Dr. Furberg testified that he casts a

wide net and then looks for signals and trends, in the same manner that the FDA completes a review. *Id.* at 105:1-6. Clinical trial data, regulatory materials and briefing documents, medical literature, and internal Pfizer documents were all relevant to his review. Tr. 105:7-107:16.

54. Based on the information available to Pfizer, Dr. Furberg concluded, to a reasonable degree of medical and scientific certainty that, although not required to raise a sufficient safety issue, there was both statistically significant and not statistically significant evidence of a risk of adverse cardiovascular events associated with Celebrex by as early as mid-1999 and with Bextra prior to its approval by the FDA in November 2001. Tr. 176:5-20; PX 174 ¶¶ 20, 67. These conclusions directly responded to the central issue of this litigation – did Pfizer knowingly make false statements regarding the CV risk of Celebrex and/or Bextra during the Class Period and satisfy the *Daubert* “fit” requirement. *Daubert*, 509 U.S. at 591-92.

II. RICHARD A. KRONMAL

A. DR. KRONMAL’S TRAINING, EDUCATION AND EXPERIENCE

55. Dr. Richard A. Kronmal, a biostatistician for more than 45 years, earned his Ph.D. in Biostatistics from the University of California, Los Angeles in 1964, and is currently a professor of Biostatistics and Statistics at the University of Washington, where he has taught biostatistics for over 30 years. PX 176 at 1, Appx. A; Tr. 308:23-24, 309:11-17.

56. Dr. Kronmal is the Director of the Collaborative Health Studies Coordinating Center at the University of Washington, which manages, runs, designs, and analyzes large clinical studies with an emphasis on cardiovascular disease. A large portion of his research endeavors over the past 40 years has been related to cardiovascular disease. Tr. 309:24-310:15.

57. Dr. Kronmal has collaborated with two large National Heart, Lung, and Blood Institute coordinating centers to study populations for cardiovascular disease over many decades.

His funding is derived almost entirely from the NIH, in the approximate amount of \$10 million annually. Tr. 310:9-23; 311:7-13.

58. Dr. Kronmal has served as: a) a consultant for the National Heart, Lung and Blood Institute, b) a member of an FDA Advisory Committee, c) Chairman of the FDA Advisory Committee on cardiovascular and renal diseases, and d) a consultant to a number of pharmaceutical companies. Tr. 313:11-315:12.

59. Dr. Kronmal has: (a) served on more than twenty (20) DSMBs, the purposes of which are to ensure the safety of patients participating in clinical trials and to monitor them for possible early termination due to undue risks; and (b) reviewed medical research papers and published more than 240 peer-reviewed articles in medical journals, such as *The New England Journal of Medicine*. PX 176 at 1-3; Tr. 315:16-316:19.

B. DR. KRONMAL'S TESTIMONY IS THE PRODUCT OF A RELIABLE METHODOLOGY

1. Dr. Kronmal's Analytical Method Is Appropriate And Reliable

60. To address the issue of the information on the CV risks of Celebrex and Bextra available to Pfizer prior to December 16, 2004, Dr. Kronmal used well-recognized statistical methods, such as the Cox Proportional Hazards Model (PX 176 at 9) and time-to-event analyses (PX 193 at 279:20-22), to analyze the data available to Pfizer prior to December 2004, including: (a) patient data and internal Pfizer reports and (b) results of other COX-2 inhibitor clinical trials published during the time period, such as VIGOR. PX 176 at 7-8; Tr. 326:6-21, 436:18-22.

61. All of Dr. Kronmal's conclusions properly rely on calculations using inputs from Pfizer's clinical study reports and SAS clinical trial data, which are testable with known error rates. PX 176 at 8-25. The methods and statistical tools Dr. Kronmal used in his analysis are the same as he uses in his day-to-day practice as a biostatistician. Tr. 356:15-19.

62. Short-term clinical trials in low-risk populations result in low statistical power (PX 176 at 8; Tr. 352:10-24), and therefore it was reasonable and appropriate for Dr. Kronmal to place greater emphasis on clinical trials: (a) of sufficient length, with higher numbers of subjects and longer follow-up time; and (b) conducted in populations with high enough risk of CV events to be informative. PX 176 at 7-8, 11, 18-20; Tr. 352:10-24.

2. Dr. Kronmal's Utilization Of Endpoints Is Appropriate And Reliable

63. In assessing Pfizer's clinical trial data for Celebrex and Bextra, Dr. Kronmal reasonably utilized as endpoints for his analysis heart-related events, such as MI, that are generally accepted by experts in the field. PX 22; PX 172; PX 204 at 107:14-20; PX 201 at 419:- 420:8.

64. Publicly-available clinical trial data that was available prior to December 2004, revealed no evidence of excess risk of stroke associated with the use of COX-2 inhibitors. Specifically, in 2000, the VIGOR study of the COX -2 inhibitor Vioxx demonstrated a statistically significant association between the use of Vioxx and heart-related events, PX 212; PX 848 at 1526, but no such association between the use of Vioxx and cerebrovascular events, such as stroke. Tr. 327:12-20, 328:3-9, 334:12-18; PX 848 at 1523.

65. It was scientifically reasonable for Dr. Kronmal to select heart-related events, such as MI, as endpoints for his analysis because that was the major signal in VIGOR, as well as the other Vioxx studies. Tr. 328:12-329:8, 350:16-23. Dr. Kronmal also used (but did not restrict himself to) the endpoints as defined by Pfizer from the data presented in the various clinical reports. Tr. 350:10-15.

66. In fact, Dr. Kronmal opined that in situations in which the reliable clinical trial data demonstrates a statistically significant excess risk of heart-related events associated with the use of a particular drug, but fails to demonstrate any excess risk of cerebrovascular events

associated with the use of that drug, selection of a composite endpoint, such as the Anti-Platelet Trialists' Collaboration ("APTC") endpoint, which combines *both* heart-related and cerebrovascular events, can have the cumulative effect of "watering down" the strength of the statistical association between use of the drug and the composite endpoint to a level that fails to achieve statistical significance. PX 22 at 1023-1024; Tr. 328:12-329:8; PX 191 at 2.4.

67. With respect to Celebrex, an internal Pfizer Cardiovascular Safety Summary memorandum dated July 14, 1999 included several of the same categorizations of adverse CV events that Dr. Kronmal utilized in his analysis of the results of the ALZ-001 study. PX 1270 at 6; Tr. 346:10-21.

68. With respect to Bextra, Pfizer itself grouped its Bextra clinical trial findings into the cardiovascular thromboembolic ("CT") endpoint (myocardial, cerebrovascular and peripheral vascular events) in its published study reports, and, as a result, it was reasonable for Dr. Kronmal to include CT as an endpoint in his analysis of Bextra clinical trial data. PX 26 at 34-35; PX 1257 at 16; PX 176 at 9; Tr. 470:23-472:7.

C. DR. KRONMAL'S TESTIMONY IS BASED UPON RELIABLE DATA

69. In forming his opinions, Dr. Kronmal was provided with raw SAS patient data⁶ and other information available to Pfizer prior to December of 2004 including, but not limited to, clinical study reports and protocols for a substantial number of randomized clinical trials. Dr. Kronmal reasonably chose to focus on, *inter alia*: (a) for Celebrex, the ALZ-001 study and the OA/RA studies; (b) for Bextra, the two coronary artery bypass graft studies (CABG-I and CABG-II), and (c) the Cancer Pain study. PX 176 at 3-4, 7-8; Tr. 341:1-5.

70. Many of Pfizer's Celebrex and Bextra clinical trials, including the ALZ-001, CABG-I, and OA/RA studies, were not designed to test drug safety – rather, they were designed

to test efficacy. As a result, the fact that these studies demonstrated a statistically significant association between Celebrex and/or Bextra use and CV risk should have put Pfizer on heightened notice of a CV safety concern. PX 176 at 18-20; PX 157 at 1-2.

71. In rendering his opinions, Dr. Kronmal also relied upon peer-reviewed literature published in medical/scientific journals, internal Pfizer documents, and documents obtained from FDA websites, reliance upon which Defendants concede is proper. PX 186 at 1-34; PX 179 App. B at 1-10; PX 182 App. 3 at 1-12; PX 181 App. B at 1; PX 180 Ex. 3 at 1-9; PX 176 at 4; Tr. 441:5-9.

D. DR. KRONMAL'S OPINIONS ARE THE PRODUCT OF THE APPLICATION OF SOUND METHODOLOGY TO RELIABLE DATA

1. Dr. Kronmal's Celebrex Opinions

a. The Alzheimer's Study

72. Dr. Kronmal's analysis of both the raw SAS patient data and the ALZ-001 study report resulted in the following conclusions: (a) there were twenty-seven (27) patients with heart-related events (*i.e.*, CV disorders, heart rate and rhythm disorders, and myocardial, endocardial and valve disorders) in the Celebrex treatment group versus one (1) in the placebo group with a relative risk of 13.32 (a 1,332 percent greater risk than placebo) at a p-value of <0.0002 (a highly statistically significant finding); and (b) 20 patients with serious adverse events (*i.e.*, CV disorders and myocardial, endocardial and valve disorders) in the Celebrex treatment group versus zero (0) in the placebo group, also a statistically significant finding. PX 33 at 73-76; PX 176 at 22; Tr. 416:5-12; Kronmal Dem. 4, 7.

73. Dr. Kronmal opined that the ALZ-001 study is statistically valuable because: (a) there was a low dropout rate among subjects; (b) it was the largest placebo-controlled study of

⁶ SAS data is more extensively described below. *See infra* § III.C.

Celebrex up to that point in time; (c) it was conducted in a vulnerable population at higher risk for CV events; and (d) it tracked participants to the end of the study. PX 74 at 2-3; PX 193 at 266:9-14; PX 176 at 20-21; Tr. 324:7-325:18.

b. The OA/RA Studies

74. The 15 clinical trials conducted between 1995 and 1998 known as the “OA/RA Studies” would not have been expected to have sufficient “power” to demonstrate the existence of a statistically significant CV safety risk because they were designed to test only the efficacy of Celebrex: (a) the treatment durations were short, with the longest placebo-controlled trial lasting only 12 weeks; (b) the studies were in populations with low risk for CV events; and (c) the follow-up of participants was poor, and there were large dropout rates, conditions that can bias the results for determining the risk of CV events if the reason for dropping out is related to the risk of CV events. Tr. 345:3-5; Kronmal Dem. 1; PX 12 at 35-36, 77-79; PX 193 at 217:3-9, 394:20-23; PX 176 at 18-20.

75. Nonetheless, when the OA/RA Studies’ adverse event findings are categorized for heart-related events in the same manner that Pfizer presented them in the 1999 Safety Memo, the results demonstrate a statistically significant elevated risk of heart-related events, with a p-value of 0.003. PX 1270 at 6; Tr. 348:1-11.

76. Dr. Kronmal found that when the analysis is restricted to studies of 12 weeks or greater, at Celebrex doses of 200 mg or greater against placebo, there are eight (8) MIs observed in the Celebrex group and one (1) MI observed in the placebo group. Therefore, the risk ratio for Celebrex is 2.6, 260% greater risk than placebo with a 95% confidence interval 0.35-115.44. PX 176 at 19-20. This is similar to the Vioxx studies. When placebo and naproxen groups are combined into a single group as the comparator, the risk ratio for Celebrex is 5.90 (95% confidence interval 0.95-36.74). The p-value for this comparison is 0.06. *Id.*

77. Despite the limited power of the OA/RA Studies, the fact that they demonstrated statistically significant CV risks highlights that it was reasonable and appropriate for Dr. Kronmal to conclude that the evidence of excess CV risk seen in these studies was a serious cause for concern from a safety perspective. Tr. 348:8-24; PX 176 at 19.

2. Dr. Kronmal's Bextra Opinions

a. The CABG-I Study

78. The CABG-I trial, completed in June 2000, was designed to study the efficacy – not the safety – of Bextra and its intravenous form parecoxib (which is converted in the body to Bextra within minutes after injection). DX 1590 at 3-4; PX 176 at 8; *see also* Tr. 161:4-12. Pfizer and the FDA have stated that parecoxib and valdecoxib are in fact the same compound for safety testing purposes. PX 214 at 1; Tr. 607:1-608:4, 608:9-609:2.

79. CABG-I is a statistically valuable clinical trial for, *inter alia*, the following reasons: (a) it was conducted in a patient population at high risk for CV events; (b) it was one of the only Bextra clinical studies available to Pfizer in 2000 which had the potential to provide useful CV risk data; and (c) it was a randomized placebo-controlled study. Tr. 352:15-24, PX 26 at 1; PX 176 at 8.

80. When analyzed using the CT endpoint Pfizer selected for its CABG-I study report (*see* PX 26 at 9), Dr. Kronmal found that the relative risk associated with Bextra was 4.21 at a p-value of 0.054, a result that (a) is consistent with what was observed in the VIGOR study during this same time period, and (b) should have raised serious concerns within Pfizer. Tr. 350:24-351:7; PX 176 at 9.

81. In fact, with respect to CABG-I results, Pfizer admits that “[t]here was a [statistically] *significantly (p<0.05) greater incidence of cardiovascular/thromboembolic events* (myocardial infarction, ischemia, cerebrovascular accident, deep vein thrombosis and pulmonary

embolism) detected in the parecoxib/valdecoxib treatment group compared to the placebo/placebo treatment group for the IV dosing period (2.2% and 0.0% respectively) and over the entire study period (4.8% and 1.3% respectively).” PX 779 at 5 (emphasis added).

82. Defendants’ expert, Dr. Barry Massie, agreed that the CABG-I results are statistically significant. Tr. 800:24-801:9.

b. The CABG-II Study

83. In January 2004, Pfizer completed CABG-II, a second clinical study designed to evaluate the efficacy and safety of Bextra in patients who had undergone CABG surgery. PX 67.

84. With respect to the CABG-II results, Pfizer admits that “[a] significantly ($p=0.033$) greater incidence of events in the cardiovascular/thromboembolic category was detected in the parecoxib/valdecoxib treatment group (2.0%) compared to the placebo/placebo treatment group (0.5%).” PX 779 at 5; PX 831 at 2.

85. Published in *The New England Journal of Medicine* in March 2005, the CABG-II study results grouped the adverse event data into clinically relevant adverse events (“CRAEs”). The two Bextra treatment groups had a statistically significant excess risk for CRAEs ($p<0.02$ for both comparisons to placebo). Further, the relative risk for a CV event for the placebo/valdecoxib treatment group was 2.03 (95% confidence interval=0.5-8.1), and for the parecoxib/valdecoxib treatment group was a statistically significant 3.7 (95% confidence interval=1.0-13.5, p -value of 0.03), as compared to the placebo treatment group. PX 101 at 1, 4, Tbl.3; PX 67 at 107; PX 176 at 14.

86. CABG-II is particularly relevant to the evaluation of CV risk because: (a) subjects were at high risk for CV events; (b) it serves as a comparison to CABG-I; (c) it was a randomized placebo-controlled study; and (d) it had greater power to assess CV risk. PX 67 at 4; PX 176 at 8, 15.

87. Dr. Kronmal found that the two CABG-II treatment groups demonstrated a statistically significant excess risk for CRAEs with a p-value of 0.02 for both comparisons to placebo. PX 67 at 107; PX 176 at 14.

c. The Cancer Pain Study

88. The Valdecoxib [Bextra] Analgesic Efficacy in Cancer Pain Study (the “Cancer Pain Study”) was a 12-week randomized study comparing Bextra to placebo, which was “designed to evaluate the analgesic efficacy of [Bextra] in patients with chronic pain due to cancer or as a result of prior cancer therapy.” PX 480 part 1 at 3; PX 176 at 13.

89. In analyzing the Cancer Pain Study, Dr. Kronmal, like Pfizer, focused on the “total mortality” endpoint, Tr. 353:3-10, which is a reliable end point that leaves no possibility for misclassification. Tr. 428:20-24; PX 480 part 2 at 75-76.

90. Of the 118 patients in the Bextra treatment arm of the Cancer Pain Study, Dr. Kronmal found there were 26 deaths (22%), compared with 12 deaths among the 119 patients in the placebo treatment arm, a statistically significant difference, yielding a p-value of 0.012. PX 53 at 75; PX 176 at 13; Tr. 353:3-21.

E. DR. KRONMAL’S CONCLUSION – THAT THERE WAS AVAILABLE TO PFIZER STATISTICALLY SIGNIFICANT EVIDENCE ON THE CV SAFETY ISSUES WITH CELEBREX AND/OR BEXTRA AS EARLY AS 1999/2000 – SATISFIES THE DAUBERT FIT REQUIREMENT

91. Dr. Kronmal was asked: (1) to determine whether there was statistical evidence of CV risk associated with Celebrex and Bextra available to Pfizer prior to December 2004; and (2) to review Pfizer’s clinical trial data for these drugs in the same way he would had he been asked to do so by Pfizer. PX 193 at 49:24-50:12; PX 176 at 3-4.

92. In seeking to answer this question, Dr. Kronmal found that: (a) in 1999, the ALZ-001 study demonstrated a statistically significant association between use of Celebrex and

heart-related events; (b) in 1999, the OA/RA Studies demonstrated a statistically significant association between use of Celebrex and heart-related events; (c) in June 2000, the CABG-I study demonstrated a statistically significant association between use of Bextra and CV events; and (d) in January 2004, the CABG-II study demonstrated a statistically significant association between use of Bextra and CV events and CRAEs. Tr. 343:24-344:4, 348:8-24, 355:21-356:13, PX 176 at 4, 16-17, 24-25.

93. Thus, Dr. Kronmal concluded that there was strong evidence by as early as 2000 that Celebrex and Bextra pose substantial CV risk. Tr. 355:21-356:13; PX 176 at 4.

94. Dr. Kronmal's testimony regarding the existence of a statistically significant association between the use of Celebrex and/or Bextra and adverse CV events prior to December 2004 has a valid scientific connection to the facts of the case and will assist the trier of fact to understand the relevant evidence. *Daubert*, 509 U.S. at 591-92; Tr. 355:21-356:13.

III. DAVID MADIGAN

A. DR. MADIGAN'S TRAINING, EDUCATION AND EXPERIENCE

95. Dr. David Madigan is a statistician who currently holds the position of Department Chair of Statistics at Columbia University. Tr. 448:10-11; PX 175 at ¶ 6.

96. Dr. Madigan's past experience includes assistant/associate professor positions at University of Washington and various teaching positions at Rutgers University, including Director of the Rutgers Institute of Biostatistics and Dean of Physical and Mathematical Sciences. Tr. 449:4-22; PX 175 at ¶ 6.

97. Dr. Madigan has published more than 100 technical papers on Bayesian statistics, biostatistics, statistical graphics, Monte Carlo methods, computer-assisted learning, information retrieval, and text mining and currently is serving a term as the Editor-In-Chief of *Statistical Science*, 2008-2010. PX 175 at ¶ 6.

98. Dr. Madigan was elected Fellow of both the Institute of Mathematical Statistics and the American Statistical Association and was the 36th most cited mathematician worldwide from 1995-2005. PX 175 at ¶ 6.

99. For three years, Dr. Madigan oversaw a computational epidemiology program at DIMACS, a multidisciplinary research center at Rutgers, that focused on post-marketing drug safety surveillance and statistical methodology. Tr. 451:1-21.

100. Dr. Madigan is the senior statistician with the Observational Medical Outcomes Partnership (OMOP), a public-private partnership designed to help improve the monitoring of drugs for safety. OMOP is conducting a two-year initiative to research methods to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market among the pharmaceutical industry, academic institutions, non-profit organizations, the FDA and other federal agencies. Tr. 452:11-453:9; PX 194 at 23:23-24:12.

101. Dr. Madigan has served as a consultant for various pharmaceutical companies including Wyeth, Novartis and Pfizer, has conducted meta-analyses for the pharmaceutical industry, and has performed other analyses similar to what he produced in this litigation for other pharmaceutical companies, in the context of a private consulting relationship.⁷ Tr. 485:16-486:18, 454:10-23; PX 175 at App. A p. 55; Tr. 650:1-3.

B. DR. MADIGAN USED A RELIABLE AND WIDELY-ACCEPTED STATISTICAL METHODOLOGY THAT IS VIRTUALLY IDENTICAL TO TESTED TECHNIQUES HE USED IN PRIOR LITIGATION AND IN PEER-REVIEWED WORK

102. In work in this litigation (his initial report was submitted on March 12, 2009), Dr. Madigan's primary statistical method was the Cox Proportional Hazard Survival Model ("Cox Model"). Tr. 483:22-484:25, 644:16-19.

103. Dr. Madigan utilized the Exact Method and the Cochran-Mantel-Haenszel (“CMH”) Methods as his secondary methods. Dr. Madigan utilized the CMH method when there was a small number of events analyzed because the Cox Model gives rise to problems when applied to a small number of events. The Exact Method is a sensitivity analysis and a variant of the CMH method. Tr. 484:15-485:3, 486:1-3, 486:6-9, 645:4-8; PX 175 at ¶ 9.

104. The COX model, the CMH model and the Exact Method are reliable and accepted statistical methods that Dr. Madigan (and Pfizer) has used outside of this litigation in both his academic work and in connection with consulting for the pharmaceutical industry on drug safety issues. Tr. 484:21-485:6, 485:15-486:18, 645:4-8, 643:1-644:7 (Referring to pending Vioxx publication using same statistical methods and approach); PX 175 at 39-53; PX 106 at Cele IND 48395 00007975, Cele IND 48395 00007993, Cele IND 48395 00008012 (Pfizer IND using CMH and Fisher Exact Test); PX 517 at 39 (Pfizer protocol using Fisher Exact Test); PX 523 at 33 (Searle Clinical Protocol using CMH).

105. In utilizing the statistical methods described above, Dr. Madigan took into account patient-year exposure to the drug. Tr. 647:8-21. Dr. Madigan completed his analysis based on the number of events and the length of time each patient was exposed to the drug. *Id.* at 647:13-19; PX 195 at 134:22-25. This is the most appropriate way of doing this type of analysis. Tr. 647:8-21; PX 194 at 72:13-73:23. *See also* PX 190 at ¶ 30; PX 176 at 19.

106. Dr. Madigan used study stratification in his analysis. Dr. Madigan stratified by both drug indication and by study block in separate analyses, and presented the p-value for both of these stratifications in his report. Tr. 641:5-20; PX 175 at ¶¶ 9-10.

⁷ Dr. Madigan has previously consulted for Pfizer, performing a meta-analysis on a neurological drug. This meta-analysis was incorporated into a Pfizer FDA submission, which is available on the FDA website. Tr. 650:4-652:9; PX 175 at App. A. p. 55.

107. Dr. Madigan performed an analysis in the Vioxx litigation in which he used the same statistical methods described above. That analysis has gone through a rigorous peer-review process and has been published in the Archives of Internal Medicine.⁸ Tr. 538:18-24, 643:2-21, 647:1-649:8; PX 194 at 14:22-15:8.

108. In October 2009, Dr. Madigan obtained information that allowed him to determine the exact statistical methods utilized by Pfizer in its 2005 Meta-Analysis submitted to the FDA, EMEA and Health Canada. Tr. 512:6-9; PX 761 at ¶¶ 6-7, 9. Using the Pfizer methods, Dr. Madigan performed additional analyses in a Declaration submitted to Defendants on October 10, 2009. Tr. 505:3-5; PX 761 at ¶¶ 1-2, 8.

109. Dr. Madigan included, in his October 2009 analysis, four deaths that were not included in the analysis in his March 2009 Report. *Id.* Dr. Madigan did not previously include these deaths primarily because the Pfizer data upon which he relied did not include any information on the cause of death, and in three of the four cases did not include a date of death. PX 761 at ¶ 8; Tr. 530:4-6.

110. In the October 2009 Declaration, in addition to the statistical methods described above, Dr. Madigan analyzed information that he had obtained from data files provided by Pfizer using the same statistical techniques that Pfizer had used in connection with the Pfizer 2005 Meta-Analysis. PX 761 at ¶¶ 5-11; Tr. 514:21-515:30, 521:14-522:7. The Pfizer methods were similar to the methods Dr. Madigan utilized in his March 2009 report, but as described above, Dr. Madigan also used a concept known as stratification by study block. Tr. 514:21-515:8, 521:14-20, 641:5-17.

⁸ While the article had not yet been published during the *Daubert* hearing, it was subsequently published in November 2009. Ross, Joseph, Madigan, *et al.* "Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data," *Arch. Int. Med.* 2009; 169(21): 1976-1985.

111. Using the data from Table 5.1.2.1 of the Pfizer 2005 Meta-Analysis, Dr. Madigan also was able to prepare an analysis of the relative risk for the myocardial thromboembolic (“MT”) endpoint (using Pfizer statistical methods and Pfizer-created data) for 200 and 400 mg total daily dose for each year from 1999 to 2004. Tr. 514:21-25; PX 761 at ¶ 11; PX 106 at 88.

C. THE DATA UNDERLYING DR. MADIGAN’S STATISTICAL ANALYSIS IS VALID AND WOULD BE RELIED UPON BY REASONABLE EXPERTS

1. Underlying Data Sources

112. Dr. Madigan utilized credible data and methods to complete his analysis in this litigation because he relied on Pfizer’s physicians and Pfizer’s data to determine what information was available to Pfizer. Tr. 880:14-881:2; Tr. 647:4-6.

113. Dr. Madigan used Pfizer clinical data (referred to as “SAS data” or “SAS files”) that existed during the Class Period for his analysis of Celebrex. Tr. 457:4-11, 530:22-24, 636:9-13, PX 175 at ¶ 8. SAS data is widely used to document clinical study results. Tr. 457:16-23, 341:1-8.

114. SAS data is the official record of a clinical trial, consisting of reported information by the study site investigators to the company conducting the clinical trial, in this case, Pfizer. Tr. 457:16-23, 477:3-25, 530:22-531:5. These records contain separate spreadsheets for demographic information and adverse event information, which is standardized using specific terms, for all the clinical trials. Tr. 457:16-458:5, 478:11-19; PX 194 at 53:12-15.

115. Dr. Madigan’s approach in utilizing the SAS data files was to use individual patient data. Tr. 458:16-21, 646:14-16; PX 175 at ¶ 10. Individual SAS patient data includes comprehensive information about each patient including when the patient was randomized, when they completed the study, and a timeline of any event suffered by them during the study. Tr.

458:22-459:7. The individual SAS patient data approach requires the statistician to utilize the individual records of each patient, not just the global statistics or cumulative, summary statistics. Tr. 646:18-20.

116. The individual patient data approach is a wholly proper way to do a meta-analysis. Tr. 341:1-8, 646:14-25; PX 148 at 118, 120; PX 126 at 769.

2. Dr. Madigan Included All Studies For Which Pfizer Provided Data

117. In applying an individual patient data approach, Dr. Madigan analyzed all placebo-controlled studies for which Pfizer provided SAS data. Tr. 461:7-12, 462:17-19; PX 175 at ¶ 14.

118. To analyze the risks associated with Celebrex appropriately, Dr. Madigan specifically excluded NSAID-controlled studies, because comparison to placebo is most germane to the question of risk. Tr. 460:20-461:6; PX 175 at ¶ 15, PX 107 at 7, 10. Nonetheless, Dr. Madigan's meta-analysis included even more studies than Pfizer utilized its own 2005 Meta-Analysis. Tr. 461:17-20, 658:24-659:10.

D. DR. MADIGAN SELECTED VALID ENDPOINTS

119. Dr. Madigan's analysis included four endpoints: (1) Hard CHD; (2) Myocardial Thromboembolic Events ("MT"); (3) Cardiovascular Thromboembolic Events ("CT"); and (4) CV Mortality. Tr. 462:25-463:4; PX 175 at ¶¶ 16-18; PX 194 at 87:23-88:12.

120. Dr. Madigan selected multiple endpoints so he could answer both broad and narrow questions with regard to the CV risk posed by the use of Celebrex. Tr. 535:12-16.

1. Three Of The Four Endpoints Used By Dr. Madigan Were Developed By Pfizer To Determine The Cardiovascular Safety Of Celebrex

121. The MT, CT and CV Mortality endpoints utilized by Dr. Madigan were also utilized by Pfizer in the Pfizer 2005 Meta-Analysis, which it submitted to various governmental

regulatory agencies around the world (including the FDA). Tr. 463:7-13, 536:1-6, 638:25-639:5, 866:8-10, 874:12-18, 876:22-24; PX 761 at ¶¶ 8-9; PX 1240 at EMEA 10000017693; PX 1257 at 16-17; PX 175 at ¶¶ 16-18.

122. Dr. Madigan, at all times during this litigation, used the MT, CT, and CV Mortality endpoints as these endpoints were defined by Pfizer in its June 2005 submission to Health Canada (the Canadian equivalent of the FDA). Tr. 863:15-865:4, 876:14-16, 655:5-22; PX 1241 at 28-29; PX 1257 at 16-17.

123. The purpose of the Pfizer 2005 Meta-Analysis, submitted in the spring of 2005 to Health Canada and other governmental regulatory bodies, was to address the very substantial regulatory issues that had arisen regarding the safety of COX-2 inhibitors following the withdrawal of Vioxx from the market in September 2004 because of CV issues. PX 1257 at 7-8. These issues were of enormous world-wide importance because of the widespread use of COX-2 drugs and the Pfizer meta-analyses were a critical component of Pfizer's effort to answer regulators' concerns regarding the safety of this class of drugs. *Id.* Thus, these endpoints reflect what Pfizer itself determined were reasonable and reliable means to assess the CV safety of Celebrex. *See* PX 1241 at 28-31; PX 1257 at 12.

2. Dr. Madigan's Hard CHD Endpoint Is A Widely-Used CV Endpoint

124. Dr. Madigan also utilized the Hard CHD endpoint because it is a widely-used endpoint in cardiology. Tr. 476:3-8, 317:16-318:20; PX 175 at ¶ 16; PX 194 at 115:3-5; PX 206; PX 596-PX 705; PX 56 at 45. In addition to the fact that Pfizer itself used the Hard CHD in its own clinical trials and materials (PX 655-PX 658; PX 705), this endpoint was used in the Framingham Heart Study (an ongoing study, started in 1948, which identified the major risk factors for CV disease) and in many statin studies as related to heart issues. Tr. 476:3-8.

E. DR. MADIGAN USED APPROPRIATE DATA TO CLASSIFY EVENTS TO THE ENDPOINTS HE SELECTED

1. Dr. Madigan Properly Classified Non-Fatal Events To His Endpoints

125. The SAS data files utilized by Dr. Madigan contain a listing of all adverse events. Tr. 457:7-459:7; PX 1092. All adverse events were reported to Pfizer by the various study investigators and were then “coded” by Pfizer to a WHO Adverse Reactions Terminology (“WHOART”) medical dictionary. Tr. 477:7-25; PX 1257 at 16. Each adverse event was coded to a specific WHOART code. Tr. 478:1-5, PX 194 at 53:5-17.

126. The endpoints established by Pfizer (MT, CT and CV Mortality) were created by Pfizer using WHOART codes for non-fatal events. Tr. 490:6-11, 500:4-10, 636:9-19. Thus, for the non-fatal events, Dr. Madigan identified the appropriate WHOART codes that corresponded with the events. Tr. 498:15-19, 639:6-11; PX 194 at 150:2-15.

127. For Hard CHD, the only non-fatal event that is included in the endpoint is non-fatal MI. PX 175 at ¶ 16. Dr. Madigan identified all non-fatal MIs using WHOART codes for inclusion in this endpoint. Tr. 639:5-11; PX 194 at 193:7-17.

2. Dr. Madigan Used Reliable Data To Include Fatal Events In His Analysis

128. Because deaths are not coded using WHOART codes, Dr. Madigan needed to have an expert determine whether the deaths that occurred in the studies he reviewed corresponded to his endpoints. Tr. 480:10-19, 490:17-19; PX 761 at ¶ 12; PX 194 at 95:23-96:15. He first extracted all of the deaths by searching for every patient that had a cause of death listed in the SAS data files. Tr. 482:5-9; PX 194 at 46:11-48:14. Then, Dr. Madigan extracted the patient deaths, including a cause of death as determined at the time of the study participant’s death. *Id.*

129. Dr. Madigan created a spreadsheet with study and patient data and a cause of death for each study participant who died in any study. PX 194 at 46:9-16. The spreadsheet did not contain any information on the treatment (Celebrex or placebo) received by each participant. Tr. 482:7-13. A copy of the spreadsheet was provided by counsel to Dr. Furberg, a national leader in CV epidemiology, who classified the events to the endpoints selected by Dr. Madigan. Tr. 481:20-482:4, 638:11-15.

130. In performing his classification of adverse events, Dr. Furberg was fully “blinded” and relied on the information on cause of death that was reported by each site investigator that was included in Pfizer’s SAS database and provided to Plaintiffs by Pfizer. PX 203 at 347:2-13; PX 194 at 46:9-16.

131. In October 2009, Defendants, for the first time, produced to Plaintiffs documents setting forth how Pfizer had coded deaths to their endpoints in connection with the Pfizer 2005 Meta-Analysis provided to Health Canada, the EMEA and the FDA. Tr. 861:11-19; PX 761 at ¶ 5.

132. Upon receipt of this information, Dr. Madigan ran his analysis using his statistical methods and the Pfizer coding of deaths for the MT, CT and CV mortality endpoints. Tr. 861:11-23; PX 761 at ¶ 8; Madigan Dem. 14-18.

133. For the hard CHD endpoints in the October Analysis, Dr. Madigan utilized Dr. Furberg’s classification of deaths because Pfizer did not use that endpoint. Tr. 638:16-20.

F. DR. MADIGAN’S CONCLUSION – THAT THERE WAS AVAILABLE TO PFIZER STATISTICALLY SIGNIFICANT EVIDENCE ON THE CV RISKS ASSOCIATED WITH CELEBREX AS EARLY AS 1999 – SATISFIES THE *DAUBERT* FIT REQUIREMENT

134. Based upon the methods and data described above, Dr. Madigan concluded that the data demonstrated a statistically significant elevated risk for Celebrex each year, starting as early as 1999. Tr. 862:9-18; PX 175 at ¶ 2.

135. At the 200 mg dose, Dr. Madigan's analysis demonstrates that Celebrex was associated with an increased relative risk of CV events. The associated p-values ranged from marginally non-significant to approximately 0.1. Tr. 501:13-19; PX 761 at Ex. 1 Supp. Tbl. 11.

136. At the 400 mg dose, Dr. Madigan's analysis demonstrates that the relative risks were highly elevated ($RR > 4$) and the p-values associated with Celebrex CV risk were generally ≤ 0.05 , and were statistically significant at that level. Tr. 501:20-502:3; PX 175 at ¶ 24.

	Myocardial Thromboembolic (400 mg TDD)		Hard CHD (400 mg TDD)	
Studies Complete by End of Year	RR & 95% CI + p-value	Stratified Exact p-value	RR & 95% CI + p-value	Stratified Exact p-value
1999	4.1 (1.0,17.9) p=0.04	0.04	3.9 (0.9,16.2) p=0.05	0.05
2000	4.1 (1.0,17.9) p=0.04	0.04	3.9 (0.9,16.2) p=0.05	0.05
2001	4.1 (1.0,17.9) p=0.04	0.04	3.9 (0.9,16.2) p=0.05	0.05
2002	4.1 (1.0,17.9) p=0.04	0.04	3.9 (0.9,16.2) p=0.05	0.05
2003	3.6 (0.9,13.7) p=0.05	0.03	3.4 (1.0,11.5) p=0.06	0.04
2004	3.6 (0.9,13.8) p=0.05	0.03	3.4 (1.0,11.6) p=0.06	0.04

PX 761 at Ex. 1 Supp. Tbl. 13; Madigan Dem. 8; Tr. 501:7-15, 501:20-502:3 (Myocardial Thrombotic); PX 175 at ¶ 14; Madigan Dem. 4; PX 761 at Ex. 4 Suppl. Tbl. 7 (Hard CHD).

137. Thus, Dr. Madigan's analysis shows that higher doses (> 400 mg) of Celebrex generally result in higher RRs, indicative of a causal dose response. PX 175 at ¶¶ 21, 24; PX 761 at Ex. 1 Supp. Tbl. 13.

138. Analyzing the same studies included in the SAS data files, using Pfizer's statistical methods and event classifications, at doses of 400 mg and above, Dr. Madigan found that using Pfizer's MT endpoint demonstrated Celebrex had a relative risk of 5.9 versus placebo ($p=0.04$). Tr. 658:15-659:10, PX 761 at Ex. 2, Supp. Tbl. 37, Madigan Dem. 11-15.

139. Further, using Pfizer's statistical methods and only the Pfizer studies used in the Pfizer 2005 Meta-Analysis, Dr. Madigan found that using Pfizer's MT endpoint demonstrated

Celebrex had a relative risk of 7.1 (rounded) versus placebo. Tr. 659:11-660:11; PX 761 at Ex. 3 Supp. Tbl. 51. Madigan Dem. 16.

140. Dr. Madigan confirmed that the relative risk of 7.07 taken from the Pfizer 2005 Meta-Analysis is statistically significant at the .05 level, with a p-value of 0.035, and that this statistically significant result was evident as early as 1999. Tr. 514:2-515:8; PX 761 at Ex. 3 Supp. Tbl. 51.

Re-analysis of Pfizer Meta-Analysis, Table 5.1.2.4		
Studies Complete by End of Year	RR & 95% CI + p-value	Stratified Exact p-value
1999	7.1 (1.2,43.4) p=0.03	0.03
2000	7.1 (1.2,43.4) p=0.03	0.03
2001	7.1 (1.2,43.4) p=0.03	0.03
2002	7.1 (1.2,43.4) p=0.03	0.03
2003	7.1 (1.2,43.4) p=0.03	0.03
2004	7.1 (1.2,43.4) p=0.03	0.03

PX 761 at Ex. 3 Suppl. Tbl. 51; Madigan Dem. 18; Tr. 522:8-523:14.

141. After analyzing the data, Dr. Madigan determined that, to a reasonable degree of scientific certainty: (i) Celebrex is associated with an increased risk of CV events (Tr. 524:12-16; PX 175 at ¶ 2; PX 761 at ¶ 16); (ii) as early as 1999, placebo-controlled data in Pfizer's possession demonstrated a statistically significant increased risk of CV events associated with Celebrex (Tr. 524:17-20; PX 175 at ¶ 2; PX 761 at ¶ 16); and (iii) at least as early as 1999, Pfizer had reasonable evidence of an association between Celebrex use and CV risk. Tr. 524:21-25; PX 175 at ¶ 2; PX 761 at ¶ 16.

IV. NICHOLAS JEWELL

A. DR. JEWELL'S TRAINING, EDUCATION AND EXPERIENCE

142. Dr. Nicholas P. Jewell is a professor of biostatistics at the University of California, Berkeley ("Berkeley"), where he held the position of Chair of the University of California Graduate Group in Biostatistics from 1986-1994, and again from 2000-2007. PX

190 at ¶ 2. He has been at Berkeley for approximately 29 years, moving up the ranks from Associate to Assistant, and ultimately to Full Professor. Tr. 883:3-9; PX 190 at ¶ 2.

143. Dr. Jewell is an expert in biostatistics and works on the application of statistics to studies of adverse outcomes, or developing methods to relate risk factors to the occurrence of disease, whether infectious or chronic. Tr. at 885:20-23; PX 190 at Appx. A.

144. Dr. Jewell has taught clinical trials at Berkeley and has served on data safety monitoring boards of clinical trials. He also has performed statistical work in analyzing clinical trials. Tr. 885:11-15. Outside of his work in academia, Dr. Jewell has been a consultant to the pharmaceutical industry, helping with the design and calculation power of clinical trials. Tr. 886:7-12.

145. Dr. Jewell has authored numerous publications on the application of statistics to problems in medicine and public health including the text book, “Statistics for Epidemiology,” (2003). Tr. 884:4-6; PX 190 at ¶ 4. This text book teaches statistical methods, including the CMH Method, which are the recipe and building blocks for conducting meta-analyses. The text book is one of the most widely used statistics-for-epidemiology text books for graduate school training in the United States today. Tr. 884:4-885:9; PX 190 at ¶ 4.

146. Dr. Jewell has authored approximately 140 peer-reviewed articles in the field of biostatistics and the application of statistics to the epidemiology of chronic and infectious diseases. Tr. at 883:18-884:3; PX 190 at ¶ 4.

B. DR. JEWELL’S OPINIONS ARE BASED ON RELIABLE DATA AND METHODS

147. Dr. Jewell reviewed the expert report of Dr. Lee-Jen Wei (April 17, 2009) and concluded, to a reasonable degree of scientific certainty, that the methodologies and types of analyses presented by Dr. Wei are not commonly used in their shared field and do not support

the conclusions that he reaches. PX 190 at ¶ 1; PX 195 at 32:13-18. Those criticism are set forth, in pertinent part, in the section addressing Dr. Wei's flawed opinions below (Section V).

148. In rebutting the opinions of Dr. Wei, Dr. Jewell relied upon the concepts that he utilizes in his professional writing, his textbook, and his non-litigation consulting work. PX 190 ¶ 6.

V. WEI'S OPINION IS SCIENTIFICALLY UNSOUND AND FAILS TO ADDRESS THE CENTRAL QUESTION IN THIS CASE

149. The question presented, as framed by this Court, was whether, prior to December 16, 2004, there existed evidence known to Pfizer demonstrating a scientifically significant increased CV risk associated with Celebrex. PX 169 at 18-19; PX 134 at ¶5, PX 169 at 18:21-19:1.

150. The expert report by Dr. Wei contains the results of a meta-analysis that purports to address the above question. PX 134 at ¶¶ 5-10. In his written direct testimony, Wei identifies three main types of analyses that he performed. As his primary analysis, he states:

[I] conducted a meta-analysis of Celebrex clinical trial data from 64 clinical trials summarized by each year from 1999 through 2005, including as of December 16, 2004. For each year and as of December 16, 2004, [he] calculated a risk ratio estimating the relative risk of the APTC endpoint and each of its components (myocardial infarction, stroke and cardiovascular death) utilizing a **proportional imputation** MH [Cochran-Mantel-Haenszel] random effects model ...

PX 1293 at 14 (emphasis added). This model utilized adverse event data from the trials he included that were "adjudicated" by three cardiologists. *Id.* at 11; PX 134 at ¶ 70.

151. Wei also used a second model (he claims as a sensitivity analysis) that avoided imputation of events. PX 1293 at 15. Wei did not develop or apply this "new" method until 2007. *Id.* at 16. This second model also used the data adjudicated by the three cardiologists. PX 134 at § 70.

152. Finally, Wei “conducted study stratified analyses applying [his] methodology to Dr. Madigan’s endpoints and event counts.... The results of those analyses are displayed in Appendix D, Exhibits 17-22 and Exhibit H, Tables 27-38 of [Wei’s] report.” *Id.* at 28.

153. In fact, each of Wei’s methods are not valid because they were either not designed to, and did not, address the question presented by the Court and/or utilized improper data and unreliable statistical techniques. Tr. 887:13-25; PX 189 at 5-6.

A. SUBSTANTIAL PARTS OF WEI’S EXPERT OPINION HAVE ALREADY BEEN WITHDRAWN

154. As an initial matter, Defendants have withdrawn 23 schedules that consist of all the direct evidence that supports Wei’s supplemental and additional analyses and criticisms of Dr. Madigan’s data and endpoints. Tr. 813:25-815:13. Defendants claimed that the decision to withdraw these portions of Wei’s analysis was based on “a slight error in calculation.” Tr. 814:1. However, Defendants provided no information concerning the results of Wei’s analysis or the nature of this calculation error. As a result, it is impossible to determine whether, and to what extent, that error impacts other aspects of Wei’s analysis, or the other Defendants’ experts who have admittedly relied upon Wei’s report in reaching their own conclusions.

B. WEI’S NON-WITHDRAWN ANALYSES ARE BASED ON DATA THAT DID NOT EXIST UNTIL AT LEAST 2007, AND THUS PROVIDE NO INFORMATION AS TO THE STATE OF PFIZER’S KNOWLEDGE OF THE CARDIOVASCULAR RISKS OF CELEBREX AND BEXTRA PRIOR TO DECEMBER 16, 2004

155. Wei’s primary method (proportional imputation Cochran-Mantel-Haenszel (“CMH”) random effects model) and his second method (Wei’s new 2007 method that avoided imputation) provide no insight into the information available to Pfizer regarding CV risk associated with Celebrex and Bextra during the Class Period.

156. Wei admits that the data incorporated in those two methods were “adjudicated” by three cardiologists in connection with the meta-analysis completed in 2007, in the Celebrex products liability litigation. PX 1293 at 11; PX 1292 at 53-54; PX 204 at 217:21-219:11.

157. According to Dr. Weintraub, “[a]djudication is the process of reviewing the clinical course of participants in a clinical trial, or series of clinical trials, in order to determine whether certain serious adverse events occurred during the trial.” PX 1292 at ¶50. In 2007, after receiving the patient narratives from Dr. Milton Packer, Dr. Weintraub collaborated with two other cardiologists (Drs. Judelson and Ben-Yehuda) to review all serious adverse events in the Celebrex clinical trials and identify which events in those trials would fall within the APTC endpoint. PX 1292 at ¶53-54. The cardiologists then adjudicated the events. *Id.*

158. The outcome of this adjudication process was a new set of adverse event data classified along the lines of the APTC endpoint. Wei admits that Defendants’ experts sought to create “a very independent meta-analysis by [themselves].” Tr. 826:5-827:9; PX 204 at 217:11-20. In fact, Wei admits that Defendants’ experts never even asked Pfizer for its adjudications of CV events. *Id.*

159. Wei further admits that Pfizer would not have been able to use this re-adjudicated data, created by Drs. Weintraub, Judelson and Ben-Yehuda, in any of its analyses prior to 2005, because that information did not exist until 2007. PX 204 at 217:21- 218:3, 218:15-219:11. As a result, Wei’s meta-analysis reveals nothing about Pfizer’s knowledge of CV risk prior to December 16, 2004.

C. WEI USED INAPPROPRIATE AND STATISTICALLY IMPROPER METHODOLOGIES IN HIS TWO NON-WITHDRAWN ANALYSES

1. Wei Ignored Patient Years

160. It is widely accepted that studies underlying a specific meta-analysis must be comparable, in terms of such factors as dose, duration, and choice of control – otherwise, combining them will fail to yield a meaningful result. PX 76 at 44; PX 190 at ¶18. Thus, to perform a combined analysis of studies of widely differing treatment durations, the researcher must either: (1) appropriately weight the results of the studies using “patient-year” data; or (2) restrict the analysis to studies of similar duration. PX 190 at ¶14, 19-25, 30; PX 195 at 144:3-146:22. In the two analyses set forth in Wei’s testimony that were not withdrawn, Wei took neither of these steps, and instead, inappropriately combined studies of widely different treatment duration without properly weighing the length of time each patient was exposed to either Celebrex or placebo. Tr. 887:18-25. Consequently, as Dr. Jewell testified, Wei’s methodology produces “very serious and misleading” results. Tr. 887:13-25; *see also* PX 190 at ¶¶ 18-19, 24.

161. Of the 40 studies that Wei incorporated in his meta-analysis where the data was available prior to December 16, 2004, 26 were six weeks or less in duration. Jewell Dem. 11; Tr. 906:14-907:4. Of those 26 studies, 11 were studies of only four weeks or shorter. *Id.* Wei only selected two studies that were greater than 12 weeks in duration. *Id.*

162. Short term studies are generally designed to assess drug efficacy and are less informative when assessing drug safety. Tr. 119:4-8; Jewell Dem. 1; PX 190 at ¶ 19. Shorter duration drug studies tend to have few or no adverse events, due in part to the fact that patients are not exposed to the study drug for a long enough amount of time. Tr. 888:18-889:11. As a result, when shorter-term studies are combined with longer term studies without properly

weighing patient-year data, the resulting risk ratio is diluted and masks the true dangers associated with long term exposure to the study drug. PX 195 at 111:13-112:10; PX 190 at ¶19; Tr. 887:18-891:5, 900:12-901:9. In Wei's analysis, of the 40 studies he included, 27 had no events in either arm of the study, thereby diluting the adverse effects seen in the longer term studies. Jewell Dem. 11; Tr. 906:14-907:4.

163. To avoid such distortions, the FDA has advised that patient-year data should be incorporated in an analysis, as opposed to only using individual patient counts as Wei has done. PX 76 at 15. The FDA points out that patient-time is especially important when studies of different treatment durations are being combined: "If there is a substantial difference in exposure across treatment groups, incidence rates should be calculated using person-time exposure in the denominator, rather than number of patients in the denominator." PX 76 at 15.

164. In fact, Wei admits that Pfizer's own meta-analysis, submitted in its 2005 FDA Advisory Committee Briefing Document, followed these principles and utilized rates per patient-year at risk. PX 83 at 15; PX 204 at 221:6-222:14.

165. Wei claims that his use of his primary methodology – the CMH random-effects model – properly weights studies to account for differences in duration (PX 1293 at 11-12, 31), but that is incorrect. In fact, as Dr. Jewell demonstrated, studies with no events constitute 42.5% of Wei's analysis. Jewell Dem. 11; Tr. 902:9-903:1. As a result, Wei's methodology artificially drives the calculation of the relative risk ratio toward one (a RR of "1" means there is no difference in the rates of events experienced by the study drug and the comparator). Tr. 900:12-901:9; 904:8-15; *see also* PX 190 at ¶ 21. In fact, under Wei's analysis, his method creates the appearance of no difference between Celebrex and placebo in terms of CV risk. However, the

confidence interval he calculates wholly excludes the results of the two longest and most informative studies. Jewell Dem. 4; Tr. 894:23-895:18.

166. Moreover, in comparing Wei's methodology with that employed by Dr. Madigan, Dr. Jewell demonstrated that analyzing the exact same numbers under the experts' respective methodologies produced strikingly different results, due solely to Wei's inappropriate statistical methodology and failure to properly account for treatment duration. Specifically, applying Wei's methodology to Dr. Madigan's data (Pfizer's data) produces significantly lower risk ratios at all levels of analysis. Tr. 900:1-901:9; Jewell Dem. 5-7.

167. Wei's failure to appropriately adjust for the vast disparity in trial durations introduces bias and distortion into his meta-analysis results and precludes meaningful interpretation or conclusions. PX 190 at ¶¶ 9-11, 17-21, 30; PX 195 at 112:4-24.

2. Wei's Imputation Method, Along With His Failure To Properly Account For Trial Duration, Deliberately Masks The Cardiovascular Risks Associated With Celebrex And Bextra

168. A risk ratio cannot be computed from an individual study with zero events in both arms, because the denominator cannot be equal to zero. PX 1293 at 13. Rather than exclude zero-event studies, Wei uses "proportional imputation" to facilitate calculation of the risk ratio. PX 1293 at 13-14.

169. As Wei explains, this technique involves adding a small positive number to all outcome counts in a study in proportion to the number of subjects in each arm. PX 1293 at 13-14.⁹ This yields an estimated risk ratio equal to one. *Id.*

170. As explained by Dr. Jewell, the net effect of including all of these "imaginary events" was to dilute the estimate of relative risk associated with Celebrex and Bextra use. Tr.

890:4-891:15. To illustrate this flaw, Dr. Jewell used the known risk associated with cigarette smoking to demonstrate how combining the results from one ten-year study with multiple six-week studies with zero adverse events using the Wei method drives the calculation of the risk ratio closer to one, giving the false impression that the risks associated with smoking are much less than longer term studies have proven. Jewell Dem. 2; Tr. 891:9-892:16.

171. Applying proportional imputation in this case, 27 of the 40 studies in Wei's meta-analysis had no events, in which he imputed "imaginary events" to each outcome (*i.e.*, CV death, non-fatal myocardial infarction and non-fatal stroke) and generated risk ratios equal to one (*i.e.*, no increased risk associated with Celebrex). Tr. 893:25-895:1, Jewell Dem. 4, 11; PX 190 at ¶¶ 21, 23. He then incorporated all of these studies with artificially-constructed risk ratios equal to one in his combined analysis. Tr. 904:8-15; PX 190 at ¶¶ 21, 23.

172. As Dr. Jewell testified, including such a significant number of short-term, zero-event trials "would move the estimate[] that you get from the long-term trials where you see an adverse safety signal and move it toward 1 and make the P-value look less significant." Tr. 893:16-21; Jewell Dem. 11. In other words, Wei's proportional imputation method effectively "washed out" the higher risk ratios observed in longer term studies with real reported adverse events. *See also* PX 190 at ¶¶ 19-21, 23-24.

3. Wei's New "No-Imputation" Method Likewise Fails To Properly Weigh Short-Term And Zero-Event Trials

173. Wei also attempts to address his deficiencies involving the use of imputations and failing to account for treatment duration by employing a new and unique method, developed by him, but not published in a peer-reviewed journal until 2009. Tr. 903:3-8; *see also* PX 204 at

⁹ For example, in a study including 50 patients taking drug A and 100 patients taking drug B, Wei indicates that he would add $50/(50+100) = 0.33$ events to the patient group receiving drug A and $100/(50+100) = 0.67$ events to the patient group receiving drug B. PX 1293 at 14.

539:12-17. Wei admits that he did not develop this method until 2007 (PX 1293 at 16), and thus it could not have been used by Pfizer to determine the CV risks of Celebrex and/or Bextra prior to December 16, 2004. *See* PX 738 at 58:8-10; 213:12-14.

174. Moreover, this method is flawed in that it artificially drives relative risk results toward zero. Specifically, using Wei's own computer code, Dr. Jewell ran a set of simulated data through Wei's model and found that when a single informative study with events and a significant difference in risk between two groups is combined with just a few zero-event studies, the model makes it appear as if there is no difference between the two groups. Tr. 903:14-904:24; Jewell Dem. 8.

D. WEI'S OPINION CONCERNING THE CARDIOVASCULAR RISK ASSOCIATED WITH CELEBREX IS NOT GENERALLY ACCEPTED BY THE SCIENTIFIC COMMUNITY

175. Wei was retained by Pfizer in 2006 in the context of the products liability cases involving Celebrex to analyze CV risk. Tr. 822:5-7. Prior to his retention by Pfizer for purposes of litigation, Wei never conducted any research concerning COX -2 inhibitors or NSAIDs, or the CV risk of a drug. Tr. 819:5-820:8; PX 204 at 14:11-15:11.

176. Wei claims that his meta-analysis demonstrates that there is no reliable statistical evidence that Celebrex increases the risk of serious CV events. PX 1293 at 1-2; PX 134 at ¶ 8.

177. As an initial matter, Wei admits that his report does not reflect the risk of all heart attacks observed in the studies included in his meta-analysis. Tr. 828:8-829:21; PX 204 at 107:2-108:14. Wei further admits that it is not possible to look at his analyses – in particular, his reported results related to the myocardial subcomponent of the APTC endpoint – and determine whether Celebrex was associated with an increased risk of heart attacks. Tr. 830:4-7.

178. Further, Wei's opinion is at odds with the position adopted by major regulatory agencies and is not generally accepted by the scientific community. Wei testified that he

disagrees with the thirty-two expert advisors on the FDA 2005 Advisory Committee, who unanimously found that the available data available as of February 2005 support a conclusion that Celebrex and Bextra significantly increase the risk of CV events. PX 204 at 559:7-23. Wei also disagrees with the AHA (PX 204 at 587:4-588:14), the EMEA (PX 204 at 567:23-568:16), and the 2005 Health Canada panel (PX 204 at 576:2-577:19), all of whom state that COX-2's are associated with increased CV risk.

179. Therefore, because Wei's methodology is scientifically unsound, and applied fatally flawed methodology to faulty data, he produces distorted results that do not "fit" the question posed for expert analysis. Thus, Wei fails to meet the *Daubert* standard for admissibility, and his meta-analysis and any conclusions derived therefrom should be excluded.

VI. DEFENDANTS' OTHER EXPERTS OFFER NO SUPPORT FOR THEIR MOTION

A. DR. BARRY MASSIE

180. While Defendants' expert Dr. Barry Massie is a cardiologist who presents himself as an expert on COX -2 clinical trials, he has never authored, edited or peer reviewed an article on COX-2 inhibitors and has never authored a book on clinical trial protocols. Tr. 776:17-18, 782:11-783:23, 784:20-785:7, 785:15-20.

181. While Massie has never written an article specifically addressing COX-2 inhibitors (Tr. 777:16-19), prior to being retained in this litigation, he's published a recommendation to the medical community with regard to COX-2 inhibitors, stating that this class of drugs should ***not*** be prescribed to heart failure patients ***because of their adverse CV effects***. Tr. 778:15-21, 779:15-17 (emphasis added). At trial, Massie attempted to claim that his published guidance not to prescribe NSAIDs was not based on specific evidence, but was the result of common sense, inference and observational studies. Tr. 779:23-780:18

B. DR. WILLIAM WEINTRAUB

182. Defendant's expert Dr. William Weintraub is one of the cardiologists who performed the adjudication of adverse events analyzed by Defendant's expert Dr. Wei. Tr. 771:9-11. For the purposes of his opinion, however, he did no statistical analysis himself but merely relied on Wei's analysis. Tr. 768:3-13, 769:19-22, 771:17-20.

183. Dr. Weintraub attempted to claim that Dr. Wei's newly developed "risk difference" method has been in use for many years, but was forced to concede that it is a recent development for meta-analysis and that it did not exist prior to January, 2005. Tr. 772:23-773:24, 774:13-16. Thus, much of the analysis relied upon by Weintraub is incapable of answering the relevant inquiry in this matter.

C. DR. FRANK W. SELLKE

184. Dr. Sellke opined in his written direct that parecoxib and valdecoxib are two different drugs and thus, the results from the CABG studies cannot be extrapolated beyond the CABG population. PX 1287 at ¶ 19. However, Sellke's opinion that parecoxib and valdecoxib are two different drugs is contradicted by: (a) the FDA, Tr. 607:1-5 and 17-24; PX 214 at 1, (b) Pfizer, Tr. 608:9-19; PX 40 at 2, and (c) the 32 members of the FDA Advisory Committee, Tr. 610:15-612:12; PX 93. Dr. Sellke further opined that no CV class effect exists as to COX -2 inhibitors. Dr. Sellke's own publications, however, undermine his opinion. In a publication in the European Society of Cardiology Journal from April 15, 2005, which Sellke co-authored, Sellke admitted that, "*COX -2 painkillers may increase the risk of heart attacks, strokes and other cardiovascular problems.*" Tr. 616:23-617:8; PX 1280 at 513 (emphasis added); and that "[o]ur observation may help us to understand one of the possible causes as to why the use of COX -2 inhibitors in the clinical trial setting increased the risk of cardiovascular events." PX 1280 at 518. In a publication in the American Journal of Physiology from July 24, 2003, which

Sellke co-authored, Sellke admitted that, "*[t]here is mounting evidence suggesting a cardio-protective effect of COX-2 and potential detrimental effects of COX-2 inhibitors on the heart . . . in addition, the use of COX-2 inhibitors may result in an increased incidence of cardiovascular events and worsening heart failure.*" Tr. 615:6-22 (emphasis added).

CONCLUSION

185. For the foregoing reasons, Plaintiffs' Experts Drs. Furberg, Kronmal, Madigan and Jewell should be admitted and permitted to testify before a jury in this matter. Further, Plaintiffs have demonstrated that Dr. Wei's methodology is fatally flawed and his testimony should be excluded. To the extent they rely on Dr. Wei in forming their opinions, the remaining Defense Experts should be excluded as well.

Dated: December 4, 2009

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APPENDIX A

TO

PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

Appendix A – Defined Terms

TERM	DEFINITION
1999 Safety Memo	Pfizer's July 14, 2009 internal meta-analysis of the OA/RA studies on Celebrex safety
2005 Pfizer Meta Analysis	A meta-analysis, created by Pfizer in 2005, which was provided to multiple government regulatory agencies, including: (a) the EMEA on March 2, 2005, (b) the FDA on May 13, 2005, and (c) Health Canada on June 9-10, 2005. This meta-analysis utilized multiple composite cardiovascular endpoints to examine the CV safety of Celebrex.
AHA	American Heart Association
ALZ-001	Pfizer's Alzheimer's Study IQ5-97-02-001
APTC	Antiplatelet Trialists' Collaboration
CABG	Coronary Artery Bypass Graft
CABG-I	Pfizer's valdecoxib / parecoxib study I93-99-02-035
CABG-II	Pfizer's valdecoxib / parecoxib study PARA-0505-071
COX-2	A form of Non-steroidal anti-inflammatory drug (NSAID) that directly targets COX-2, an enzyme responsible for inflammation and pain
Cancer Pain Study	Pfizer's Valdecoxib Analgesic Efficacy in Cancer Pain Study
Class Period	October 31, 2000 to October 19, 2005
CMH	Cochran-Mantel-Haenszel random effects model
Cox Model	Cox proportional hazard survival model
CRAE	Clinically relevant adverse event
CT	Cardiovascular thromboembolic endpoint incorporating myocardial, cerebrovascular and peripheral vascular events
CV	Cardiovascular
CV Mortality	Endpoint defined by Pfizer in June 2005 submission to Health Canada as including sudden death, death not otherwise specified, and fatal cases of arteriosclerosis, atrial fibrillation, cardiac failure, congestive heart failure, coronary artery disorder, ventricular fibrillation and fatal aneurysm together with other fatal events.
DSMB	Data Safety Monitoring Board
EMA	European Medicines Agency
Exact Method	A statistical sensitivity analysis and a variant of the CMH method
FDA	Food and Drug Administration
Fisher Exact Test	A statistical significance test used with data from small sample sizes
FitzGerald Hypothesis	Theory as to why selective COX-2 inhibition could cause platelet aggregation and an increased risk of CV events.
Hard CHD	Endpoint incorporating MI and sudden cardiac death
MI	Myocardial infarction
MT	Myocardial thromboembolic endpoint incorporating death from various cardiac causes, as well as angina pectoris aggravated, cardiac arrest, circulatory failure, myocardial ischemia, myocardial rupture, ventricular tachycardia, and coronary thrombosis.
NIH	National Institutes of Health

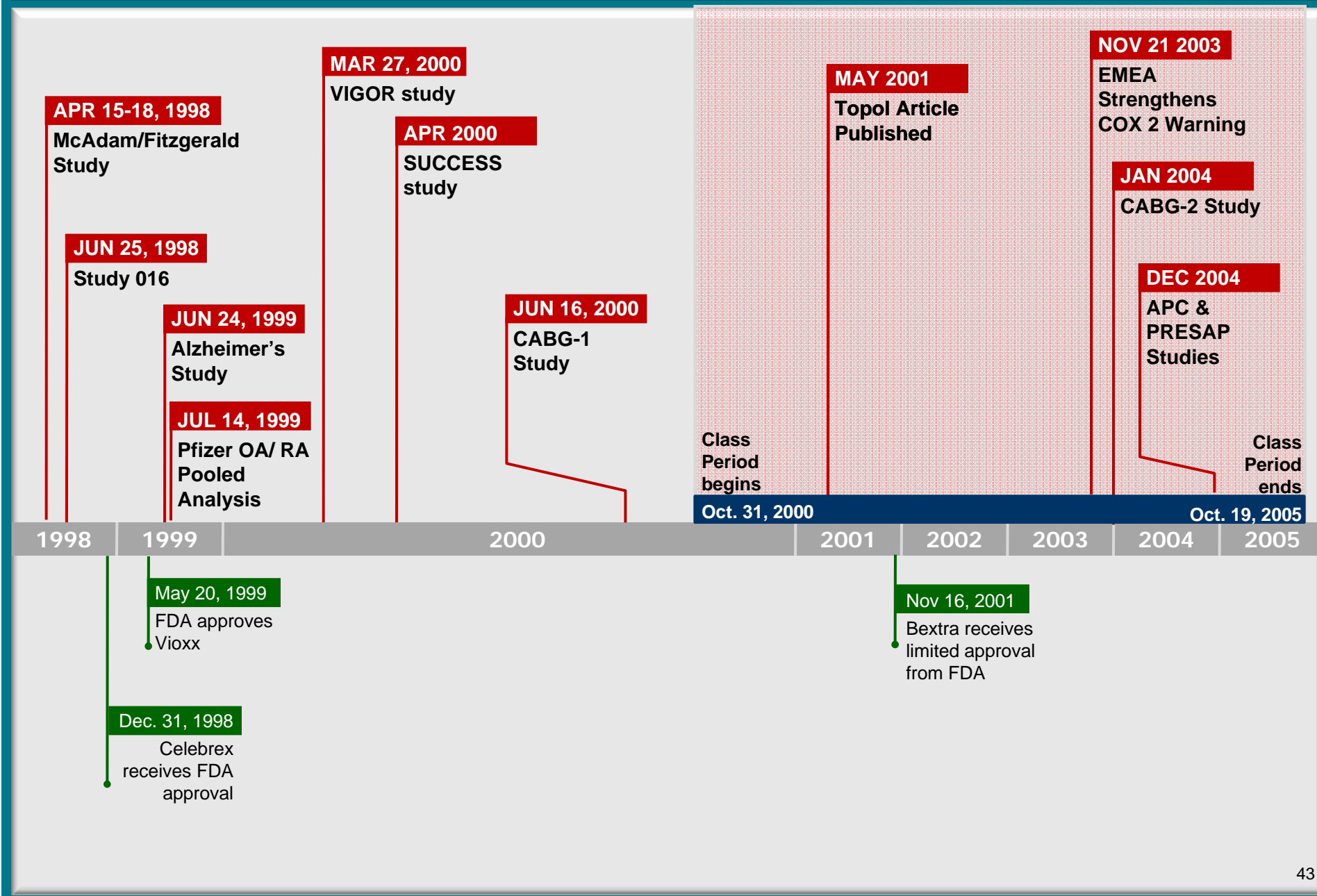
TERM	DEFINITION
NSAID	Non-steroidal anti-inflammatory drug
OA/RA	Osteoarthritis and rheumatoid arthritis
OA/RA Studies	Pfizer's OA/RA clinical trials conducted between 1995 and 1998 and analyzed by Dr. Kronmal
OMOP	Observational Medical Outcomes Partnership
RR	Risk Ratio or Relative Risk
Rule 702	Federal Rule of Evidence 702
Study 016	Pfizer's Bextra study N91-97-02-016
Study 047	Pfizer's valdecoxib study N91-99-02-047
SUCCESS	Pfizer's Successive Celebrex Efficacy and Safety Study
TDD	Total daily dose
VIGOR	Merck's Vioxx Gastrointestinal Outcome Research study
WHO	World Health Organization
WHOART	World Health Organization Adverse Reactions Terminology

APPENDIX B

TO

PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

Pfizer's Knowledge of Cardiovascular Risks Associated with Celebrex and Bextra



CERTIFICATE OF SERVICE


The undersigned, hereby certifies that a copy of the below listed document was served with the clerk of the Court using the ECF system, which will send notification of such filing to all counsel of record identified on the Court's list of registered users for the case.

- PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

I additionally certify that the counsel listed below have been additionally served by overnight mail with the same document and a set of exhibits which will be conventionally filed.

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